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Authors: Wang Xiao-Tong, Song Jia-Lin, Zhong Mei, Kang Hua-Jie, Xie Hui, Che Tong, Shu Bing, Peng Dongming, Zhang Luyong, and Zhang Shang-Shi

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Iridium-Catalyzed [4+2] Annulations of β-keto Sulfoxonium Ylides and *o*-Phenylenediamines: Mild and Facile Synthesis of Quinoxaline Derivatives

Xiao-Tong Wang[d], Jia-Lin Song[d], Mei Zhong[d], Hua-Jie Kang[d], Hui Xie[a], Tong Che[a], Bing Shu[d], Dongming Peng[e], Luyong Zhang,*[a,b,c] Shang-Shi Zhang*[a,b,c]

[a] Center for Drug Research and Development, Guangdong Pharmaceutical University, Guangzhou, 510006, China, e-mail: zhangshangshi@gdpu.edu.cn, lyzhang@cpu.edu.cn.
[b] Guangzhou Key Laboratory of Construction and Application of New Drug Screening Model Systems, Guangdong Pharmaceutical University, Guangzhou, 510006, China
[c] Key Laboratory of New Drug Discovery and Evaluation of Ordinary Universities of Guangdong Province, Guangdong Pharmaceutical University, Guangzhou, 510006, China
[d] School of Pharmacy, Guangdong Pharmaceutical University, Guangzhou, 510006, PR China
[e] Department of Medicinal Chemistry, School of Pharmacy, Hunan University of Chinese Medicine, Changsha, 410208, China

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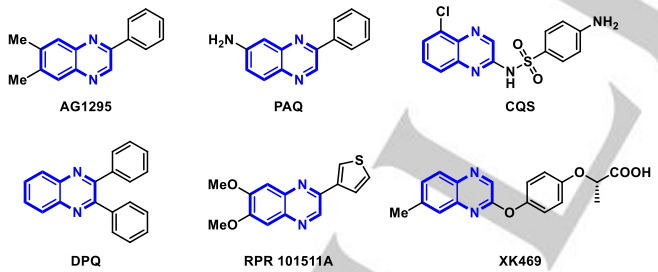
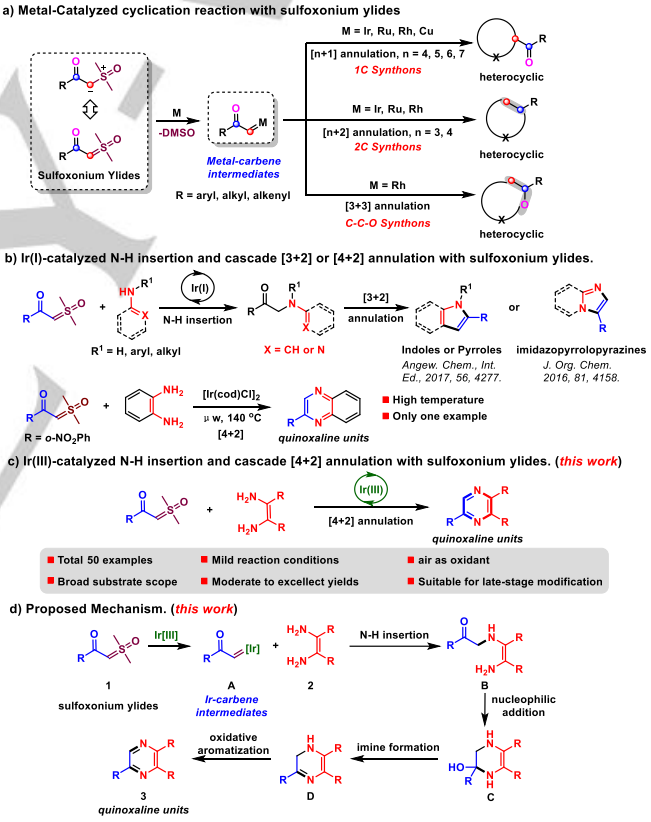
Abstract: A synthetic method for quinoxaline derivatives from the [4+2] annulation of β-keto sulfoxonium ylides and o-phenylenediamine by using $(Cp^*IrCl_2)_2$ catalyst is described. This novel protocol features mild reaction conditions, moderate to excellent yields, wide substrate scope, and high functional-group compatibility. Moreover, this cyclization strategy was successfully applied in late-stage modification for structurally complex bioactive compounds.

Quinoxaline and its derivatives are frequently encountered structural motifs in a diverse range of pharmaceuticals and bioactive compounds. Examples of bioactive compounds containing quinoxaline scaffolds include platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitors, antitumor cytotoxic agents, neuroprotective agents, and Topo-II poison, such as AG1295, PAQ, CQS, DPQ, RPR101511A, and XK469, which are shown in Scheme 1.[1] Strategies for high-efficiency synthesis of the quinoxaline skeleton by using mild conditions and readily available starting materials are in high demand.



Scheme 1. Quinoxaline cored natural and bioactive compounds.

Since first β-keto sulfoxonium ylides have been reported by the Chaykovsky group reported in the 1960s,[2] this reagent have been increasingly popular as important building blocks in organic synthesis.[3] These ylides are well-behaved and generally crystalline and bench-stable solids, and can be easily prepared in one step from the corresponding carboxylic acids or their derivatives. They can smoothly generate metallocarbene complexes by releasing a molecule of dimethyl sulfoxide as a by-product, and have been certified as alternative carbene equivalents to α-diazocarbonyl compounds. Furthermore, when compared with diazo compounds, on the one hand, it has similarly reactivity in processes such as C-H activation,[4] cycloaddition,[5] X-H insertion,[6] dimerizations,[7] among others.[8] On the other hand, their higher thermodynamic stability and security features has been demonstrated and used in industrial scale production.[9]



Scheme 2. Strategies for sulfoxonium ylides Utilization in annulation reaction.

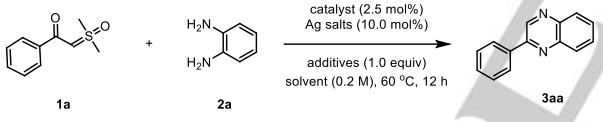
Recently, numerous research groups have been involved in the development of a new reaction of β-keto sulfoxonium ylides. In particular, those compounds have been approved as a forceful and universal synthetic tool for the organic chemists, owing to fruitful chemistries of both the sulfoxonium ylides and carbonyl moieties. While, the reported cyclization reactions of β-keto sulfoxonium ylides via metal-carbene intermediates process mainly include the following categories: 1) As one carbon synthons participates in (n+1, n = 4, 5, 6, 7) annulation reaction (Scheme 2a).[10] 2) Be known as two carbon synthons mediates (n+2, n = 3, 4) cyclization reaction (Scheme 2a).[11] 3) Be used as C-C-O synthons accomplished (3+3) cyclization reaction

(Scheme 2a).[12] In 2016, the labs of Vaitla and Shekhar first applied β-keto sulfoxonium ylides to annulation reaction via a iridium-catalyzed N-H insertion and [3+2] cyclization cascade strategy, and generating diverse heterocycles such as indoles, pyrroles and imidazopyrrolopyrazines derivates (Scheme 2b).[13] Vaitla group also realized iridium-catalyzed [4+2] annulation reaction of β-keto sulfoxonium ylides and benzene-1,2-diamine, delivering quinoxaline units in moderate yield. However, only one example was reported as well as high reaction temperature will limit the practicality of this transformation.[13b]

Based on our ongoing research interest in new reactions to β-keto sulfoxonium ylides and previous work.[14] We herein disclosed the effective Cp*Ir^{III}-catalyzed [4+2] annulation of β-keto sulfoxonium ylides with various 1,2-diaminoarenes to furnish monosubstituted quinoxaline and its derivatives elegantly through tandem cyclization strategy (Scheme 2c). This wonderful protocol proceeded by employing air as an efficient oxidizing agent, broad substrate scope, excellent functional group tolerance, moderate to excellect yields and total 50 examples was observed. What's more, it can be successfully applied to late-stage modification of drug molecules.

On the basis of a literature precedent,[13] a plausible mechanism was proposed to account for the present transformation in Scheme 2d. Firstly, β-keto sulfoxonium ylides can be activated by $(Cp^*IrCl_2)_2$ and generates the iridium carbene intermediates **A**, which is followed by coordination of 1,2-diaminoarene **2** via N-H bond insertion to form species **B**. Then, the intermediate **B** undergoes three process including intramolecular nucleophilic addition, dehydration and oxidative aromatization in turn, finally release the quinoxaline product **3**.

Table 1. Optimization of Reaction Conditions[a]



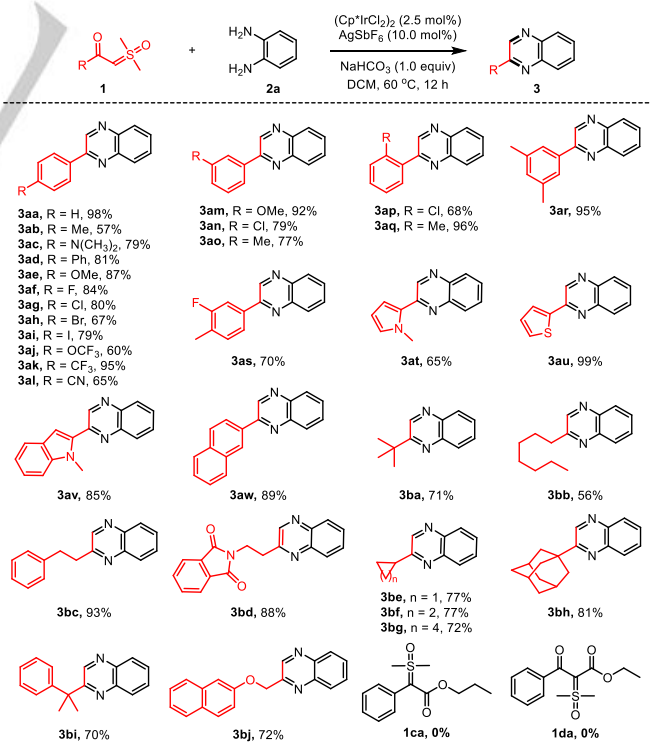
1a 2a 3aa

Entry	Catalyst	Ag salts	Additives	Solvent	Yield[b]
1	$(Cp^*RhCl_2)_2$	$AgSbF_6$	CsOAc	DCE	27%
2	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	CsOAc	DCE	47%
3	$(Cp^*IrCl_2)_2$	$AgSbF_6$	CsOAc	DCE	68%
4	$MnBr(CO)_5$	-	NaOAc	DCE	ND[c]
5	$Pd(OAc)_2$	-	CsOAc	DCE	ND
6	$(Cp^*IrCl_2)_2$	$AgSbF_6$	CsOAc	DCM	74%
7	$(Cp^*IrCl_2)_2$	$AgSbF_6$	CsOAc	THF	43%
8	$(Cp^*IrCl_2)_2$	$AgSbF_6$	CsOAc	Toluene	65%
9	$(Cp^*IrCl_2)_2$	$AgSbF_6$	CsOAc	DMF	58%
10	$(Cp^*IrCl_2)_2$	$AgSbF_6$	NaOH	DCM	34%
11	$(Cp^*IrCl_2)_2$	$AgSbF_6$	K_2CO_3	DCM	86%
12	**$(Cp^*IrCl_2)_2$**	**$AgSbF_6$**	**$NaHCO_3$**	**DCM**	**98%**
13	$(Cp^*IrCl_2)_2$	$AgSbF_6$	K_3PO_4	DCM	76%
14	-	$AgSbF_6$	$NaHCO_3$	DCM	trace
15	$(Cp^*IrCl_2)_2$	-	$NaHCO_3$	DCM	38%
16	$(Cp^*IrCl_2)_2$	$AgSbF_6$	-	DCM	75%

[a]Reaction Conditons: **1a** (0.2 mmol), **2a** (1.5 equiv), catalyst (2.5 mmol%), **Ag** salts (10.0 mmol%), additives (1.0 equiv), solvent (0.2 M), 60 °C, 12 h. [b]Isolated yield. [c]ND = not detected.

We commenced our studies by optimizing the coupling reaction conditions of sulfoxonium ylide **1a** with benzene-1,2-diamine (**2a**). When the reaction was performed in the presence of $(Cp^*IrCl_2)_2$, $AgSbF_6$ and CsOAc in dichloroethane under air atmosphere at 60 °C for 12 h, the desired product **3aa** was obtained with 68% yield (Table 1, entry 3). Other catalysts such as $(Cp^*RhCl_2)_2$, $[RuCl_2(p\text{-cymene})]_2$, $MnBr(CO)_5$ and $Pd(OAc)_2$ exhibits much lower efficiency (Table 1, entries 1-2, 4-5). Next, solvent screening experiment displayed that dichloromethane was the better solvent in the case of the $(Cp^*IrCl_2)_2$ catalyst (Table 1, entries 6-9). To further improve the catalytic efficiency of this transformation, different types of bases additives were introduced into the catalytic systems (entries 10−13). It was satisfying that the target product **3aa** could be obtained in 98% yield with employing $NaHCO_3$ as additives (Table 1, entry 12). Furthermore, the control experiment indicated that $(Cp^*IrCl_2)_2$ is necessary for this transformation (table 1, entry 14). When there is no addition $AgSbF_6$ and $NaHCO_3$ in this system, the expected annulation reaction proceeded with decreasing efficiency, and the lower product **3aa** yield was obtained (Table 1, entries 15-16).

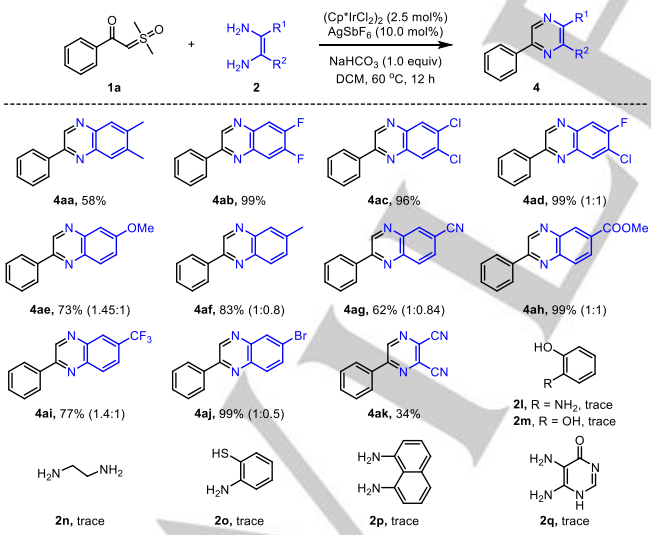
With the optimized reaction conditions established, we firstly investigated the scope and universality of this transformation by using benzene-1,2-diamine (**2a**) and a variety of β-keto sulfoxonium ylides. As shown in Scheme 3, It turned out that aromatic sulfoxonium ylide **1** bearing either electron-rich groups such as methyl (**3ab**, **3ao**, **3aq**-**3as**), dimethylamino (**3ac**), phenyl (**3ad**), methoxy (**3ae**, **3am**) or electron-deficient substituents such as halogen (**3af**-**3ai**, **3an**, **3ap**, **3as**), trifluoromethoxy (**3aj**), trifluoromethyl (**3ak**), cyano (**3al**) groups at different positions



Scheme 3. Substrate Scope of sulfoxonium ylides.

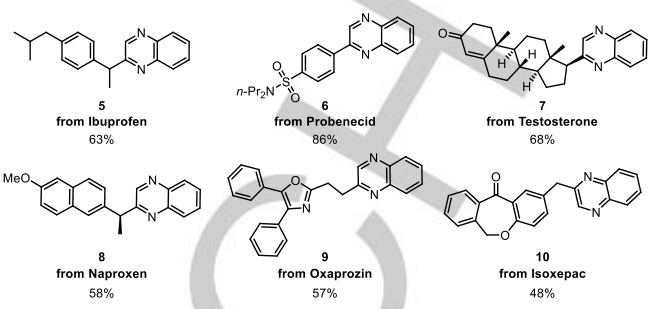
were coupled smoothly, and giving corresponding product with satisfactory yields. In addition, pyrrole-(**3at**), thiophene-(**3au**), indole-(**3av**) and naphthalene-containing (**3aw**) β-keto sulfoxonium ylides substrates were also compatible under the standard reaction conditions. Subsequently, the reactivity of alkyl sulfoxonium ylides substrates was also investigated. Under optimal conditions, different types of alkyl substituents whether branched alkanes (**3ba**, **3bi**), long-chain alkanes (**3bb**-**3bd**, **3bj**) or cycloalkanes (**3be**-**3bh**) all were acquired receivable consequence. Unfortunately, α-ester sulfoxonium ylides **1ca** and β-keto ester sulfoxonium ylides **1da** completely inhibits the reactivity, maybe the highly coordination property of di-carbonyl moiety with iridium catalyst.

The scope of the 1,2-diaminoarene **2** was examined subsequently in this reaction (Scheme 4). Various symmetric and unsymmetrical substrates was evaluated in this transformation, and most of them can be efficiently conversion to multisubstituted quinoxaline with satisfied yield. It should be pointed out that a significant electrical effects were observed, di-substituted 1,2-diaminoarene which possessed of electron-withdrawing substituents such as halogen (**4ab**-**4ad**) has been shown to have higher compatibility than those of electron-donating substituents substrates (**4aa**). Competitive experiment also demonstrated that the reaction efficiency of electro-deficient coupling parner is higher than that of electro-rich coupling parner (see SI). Furthermore, when unsymmetrical 1,2-diaminoarene are used as coupling partner, there presence two isomers in corresponding product quinazolines (**4ad**-**4aj**), respectively, which could not be isolatable on flash silica gel column chromatography for the reason of similar polarity. It is noteworthy that 2,3-diaminomaleonitrile also proved to be amenable to the catalyzed system albeit in lower yields (**4ak**). Unfortunately, other di-nucleophilicity substituted substrate are incompatible for the standard reaction conditions (**2l**-**2q**).



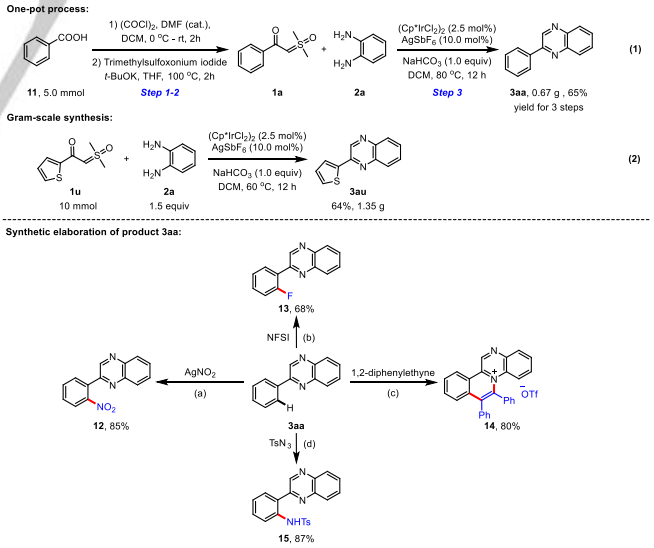
Scheme 4. Substrate Scope of o-phenylenedi-amine.

In order to demonstrate the practicability and universality of the reaction better, we applied this novel annulation protocol to the late-stage modification of drug molecules. Just as scheme 5 described, several β-keto sulfoxonium ylides which preparation from drug molecules such as ibuprofen, probenecid, testosterone, naproxen, oxaprozin and isoxepac were employed in this catalytic system, all of them generated novel bioactive entity with a new skeleton structure and potential bioactivity respectively with well-pleasing yield (**5**-**10**). Those results greatly exemplify the robustness and usefulness of this transformation for pharmaceuticals modification.



Scheme 5. Application of Iridium-Catalyzed [4+2] annulation Reaction in Late-Stage Modification.

It's worth mentioning that an unexceptionable one-pot acylation/conjugate addition/[4+2] cyclization coupling sequence was realized and a moderate but promising overall yield of 65% was obtained (Scheme 6, eq 1). Subsequently, the gram scale experiment further indicated the scalability of the reaction (Scheme 6, eq 2). In addition, synthetic elaboration of product **3aa** was performed by making the utmost of directing ability of nitrogen atoms in the quinoxaline ring (Scheme 6). Thus, treatment of **3aa** with $AgNO_2$ in presence of $Pd(OAc)_2$ catalyst delivered a 2-(2-nitrophenyl)quinoxaline **12** in 85% yield.[15] Furthermore, quinoxaline-directed ortho-monofluorination in **3aa** was easily achieved and produced **13** in 68% yield.[16] Gratifyingly, the multifunctional AEEgens product **14** could also be synthesized in 80% yield.[17] Finally, C-N bond formation reaction was accomplished by treating **3aa** with TsN_3 by the means of Cp^*Ir^{III}-catalyzed C-H activation, generated compound **15** in 87% yield.[18]



Reaction conditions: (a) **3aa** (0.3 mmol), $AgNO_2$ (2.0 equiv), $Pd(OAc)_2$ (10.0 mol%), $K_2S_2O_8$ (2.0 equiv), DCE (3.5 mL), 130 °C, 48 h. (b) **3aa** (0.2 mmol), NFSI (1.5 equiv), $Pd(OAc)_2$ (10.0 mol%), TFA (2.0 equiv), [CH_3NO_2-CH_3CN = 1:1 (v/v)] (2.0 mL), 110 °C, 12 h. (c) **3aa** (0.3 mmol), 1,2-diphenylethyne (1.2 equiv), [$RuCl_2$(p-cymene)]$_2$ (5.0 mol%), $Cu(OAc)_2.H_2O$ (2.2 equiv), TfOH (1.5 equiv), DCE (2.0 mL), 120 °C, 12 h. (d) **3aa** (0.3 mmol), TsN_3 (0.2 mmol), $(Cp^*IrCl_2)_2$ (4.0 mol%), $AgPF_6$ (16.0 mol%), PivOH (0.5 equiv), DCE (1.0 mL), 80 °C, N_2, 1 h.

Scheme 6. Synthetic application of the product **3aa**.

In summary, we have successfully realized the complementary Cp*Ir^{III}-catalyzed [4+2] annulation reaction of β-keto sulfoxonium ylides and 1,2-diaminoarene. The advantages of this reaction containing broad substrates scope, wide functional group tolerance, mild reaction conditions and compatibility for late-stage modification. Optimization of the reaction condition indicated that $(Cp^*IrCl_2)_2$ is crucial for this transformation. Futhermore, this reaction provides a new method to the synthesis of quinoxaline. Efforts to expand the utility of this coupling and to design other Cp*Ir^{III}-catalyzed cyclization reactions with β-keto sulfoxonium ylides are in progress in our laboratory.

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Keywords: sulfoxonium ylides; quinoxaline; iridium-catalyzed; [4+2] annulation; 1,2-diaminoarene

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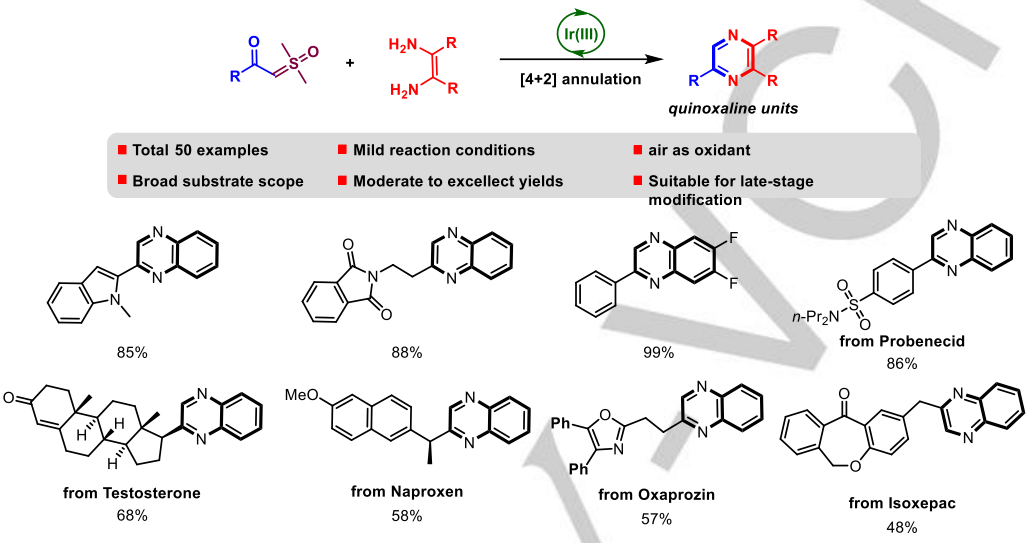
Entry for the Table of Contents

Iridium-Catalyzed [4+2] Annulations of β-keto Sulfoxonium Ylides and o-Phenylenediamine: Mild and Facile Synthesis of Quinoxaline Derivatives

Xiao-Tong Wang[d], Jia-Lin Song[d], Mei Zhong[d], Hua-Jie Kang[d], Hui Xie[a], Tong Che[a], Bing Shu[d], Dongming Peng[e], Luyong Zhang,*[a,b,c] Shang-Shi Zhang*[a,b,c]



The effective Cp*Ir^{III}-catalyzed [4+2] tandem cyclization reaction of β-keto sulfoxonium ylides and o-phenylenediamine has been reported for the first time, furnishing monosubstituted quinoxaline and its derivatives with moderate to excellent yield. This novel protocol exhibits broad substrate scope as well as feasibility for late-stage modification of drug molecules.

Key Topic: cycloaddition